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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JON A. WOLFF and VLADIMIR G. BUDKER

Appeal 2007-2711
Application 09/707,117
Technology Center 1600

Decided: January 16, 2008

Before TONI R. SCHEINER, DONALD E. ADAMS, and
LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36, and 39-42. We have jurisdiction under 35 U.S.C. § 6(b). Claims 1 and 39 are representative of the claims on appeal, and read as follows:

1. A process for delivering a polynucleotide to a skeletal muscle cell of a mammal in vivo, comprising:

- a) applying non-invasive external pressure against the skin of a limb of the mammal such that blood flow to and from the limb is impeded;
 - b) inserting the polynucleotide encoding a protein operably linked to a promoter in a solution into a blood vessel in the limb in vivo distal to the applied pressure; and,
 - c) administering immunosuppressive drugs to the mammal;
- thereby delivering the polynucleotide to the skeletal muscle cell in the limb distal to the applied pressure and expressing the polynucleotide in the skeletal muscle cell at detectable levels.

39. A process for delivering a polynucleotide to a skeletal muscle cell of a mammal in vivo, comprising:

- a) applying pressure non-invasively against the skin of the limb thereby impeding blood flow into and out of the limb;
 - b) inserting the polynucleotide encoding an expressible sequence operably linked to a promoter in a solution into a blood vessel in the limb of the mammal in vivo distal to the applied pressure;
 - c) delivering the polynucleotides to the skeletal muscle cell of the limb distal to the applied pressure; and,
 - d) expressing the polynucleotide in the skeletal muscle cell to detectable levels;
- wherein said applying, said inserting, said delivering and said expressing do not diminish subsequent use of the limb by the mammal.

We reverse.

DISCUSSION

Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36, and 39-42 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Appellants regard as the invention.

According to the Examiner, the phrase “to a skeletal muscle cell of a mammal” in the preamble of claim 1 is not commensurate in scope with the phrase “to the skeletal muscle in the limb distal to the applied pressure” in step c (Answer¹ 14). The Examiner asserts that the phrase “to the skeletal muscle in the limb distal to the applied pressure” in step c lacks antecedent basis. The Examiner argues it is “unclear if the claim is intended to deliver the polynucleotide to any skeletal muscle cell of mammal as in the preamble or to a skeletal muscle cell of a limb distal to the site of applying pressure as in the body of the claim.” (*Id.*)

The Examiner asserts that claim 1, step b, is indefinite, as the phrase “inserting the polynucleotide encoding a protein operably linked to a promoter into a blood vessel” lacks antecedent basis (*id.*). According to the Examiner, the “phrase in the body of the claim is not readily apparent from the preamble of the claim, which merely refers to ‘delivering a polynucleotide to a skeletal muscle cell of a mammal in vivo.’” (*Id.*)

“The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification.” *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Claims are in compliance with 35 U.S.C. § 112, second paragraph, “if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits.” *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1987).

We conclude that one skilled in the art would understand that the claim, when read in light of the Specification, requires that the

¹ All references to the Answer are to the Examiner’s Answer mailed July 27, 2006.

polynucleotide be delivered to a skeletal muscle cell of a limb distal to the site of applying pressure as in the body of the claim, as step (b) specifically requires “inserting the polynucleotide encoding a protein operably linked to a promoter in a solution into a blood vessel in the limb in vivo distal to the applied pressure.” The rejection is thus reversed.

The Examiner also argues that the phrase “applying non-invasive pressure” in claim 1, and the phrase “applying pressure non-invasively” in claim 39 are indefinite as “invasive” may be defined in two different ways (Answer 14-15). The Examiner cites Stedman’s Medical Dictionary, which defines “invasive” as “denoting a procedure requiring insertion of an instrument or device into the body through the skin or a body orifice. . .,” and also cites Meriam-Webster Online Dictionary, which defines “invasive” as “to affect injuriously and progressively.” (*Id.* at 15.) According to the Examiner, the Specification does not teach which scope of the term “invasive” to use, as the cuff in Example 1 was applied during a surgical procedure (*id.*). The Examiner asserts that is “is not readily apparent that the cuff was applied outside of the surgical area (only on skin) and not over the surgical area. Therefore, it cannot be determined whether pressure that does not cause injury to the leg is encompassed by the phrase. Nor can it be determined if a tourniquet that passes under the inguinal ligament in a surgical area is non-invasive because such a tourniquet does not affect the leg injuriously or progressively.” (*Id.*)

During prosecution before the Office, claims are to be given their broadest reasonable interpretation consistent with the Specification as it would be interpreted by one of ordinary skill in the art. *In re American*

Academy of Science Tech Center, 367 F.3d 1359, 1364 (Fed. Cir. 2004).

Keeping that in mind, we conclude that one of ordinary skill would interpret “invasive” in light of the teachings of the Specification in accordance with the definition provided by Stedman’s Medical Dictionary, that is, as “denoting a procedure requiring insertion of an instrument or device into the body through the skin or a body orifice.” Thus, non-invasive would require that the cuff be applied only to the skin, and not over the surgical area.

That definition finds support in the Specification. The Specification teaches that the “process includes externally impeding interior blood flow by externally applying pressure to interior blood vessels such as compressing mammalian skin by applying a tourniquet over the skin. Compressing mammalian skin also includes applying a cuff over the skin such as a sphygmomanometer.” (Specification 3.) Moreover, the Specification expressly states that “for purposes of the claims, cuff refers specifically to a device applied exterior to the mammal’s skin in a non-invasive manner.” (*Id.* at 5.)

That understanding is not contradicted by Example 8 of the Specification. Example 8 states:

Seven Rhesus macaque monkeys (5 males; 2 females) of 6 to 13.7 kg body weight underwent intraarterial injections in their limbs following anesthesia with ketamine and halothane. For the forearm injections, a longitudinal incision, ~3 cm in length, was made on the skin along the inside edge of the biceps brachii and 2 cm above the elbow. After separating the artery from surrounding tissues and veins, a 20 g catheter was inserted into the brachial artery anterogradely and ligated in place. For the lower leg injections, the procedure was essentially the same as that used in the arm, but the incision was located on the upper edge of the popliteal fossae and the 20 g catheter was inserted into the popliteal artery .

For both the arm and leg injections, blood flow was impeded by a sphygmomanometer cuff surrounding the arm or leg proximal to the injection site. After the sphygmomanometer was inflated to more than 300 mmHg air pressure, the catheterized vessels were injected with 30 ml of normal saline containing 5 mg papaverine (Sigma Co.). Five min. later, a saline solution containing 100 µg pDNA/ml solution was rapidly injected within 30 to 45 sec. For the arms, the volume of each injection was 75 ml and 90 ml in the first two animals and 120 ml thereafter. The injection volume was ~180 ml for the lower legs. The DNA solutions were injected using a nitrogen-pressurized cylinder. Two min after injection, the catheters were removed and the sphygmomanometer deflated.

(*Id.* at 23.)

Thus, the cuff was placed proximal to the injection site on the leg or the arm. When read in light of the remainder of the Specification, one of ordinary skill would not read the above passage as placing the cuff on the surgical site, but would read it as placing it in a non-invasive manner on the skin of the arm or leg.

Moreover, to interpret “non-invasive” as allowing the external pressure to be applied directly on the surgical site would be effectively reading “non-invasive” out of the claim. The claims must not be construed so broadly as to abrogate an express limitation. *In re Wilder*, 429 F.2d 447, 450 (CCPA 1970) (“[E]very limitation positively recited in a claim must be given effect in order to determine what subject matter that claim defines.”); *Texas Instruments, Inc. v. International Trade Comm.*, 988 F.2d 1165, 1171, (Fed. Cir. 1993) (“[T]o construe the claims in the manner suggested by TI would read an express limitation out of the claims. This we will not do.”).

We therefore conclude that the phrase “applying non-invasive pressure” in claim 1, and the phrase “applying pressure non-invasively” in claim 39 are not indefinite, and the rejection is reversed.

The Examiner also asserts that the phrase “wherein said applying, said inserting, said delivering and said expressing the polynucleotide do not diminish subsequent use of the limb” is unclear (Answer 15). According to the Examiner, “[i]t is unclear if the phrase is limited to the function of the limb after the procedure or if the phrase encompasses the diminished frequency of use of the limb.” (*Id.*) The Examiner argues, “contrary to the claim, it was well known that a limb that underwent surgery had diminished use right after surgery because of inflammatory responses, anesthesia and pain. Thus, the metes and bounds of the phrase are unclear and do not make sense when considering surgery recovery.” (*Id.* at 16.)

We conclude that one skilled in the art would understand the bounds of the phrase “wherein said applying, said inserting, said delivering and said expressing the polynucleotide do not diminish subsequent use of the limb” when read in light of the specification. As noted by Appellants, the Specification teaches that the monkeys “did not appear to be in any discomfort beyond that of normal surgical recovery.” (Br. 9, quoting Specification, p. 25, ll. 22-24.) Thus, the skilled artisan would understand that the phrase requires that there be no loss of use of the limb beyond that of normal surgical recovery. The rejection is thus reversed.

The Examiner asserts that the phrase “‘the polynucleotide encoding an expressible sequence operably linked to a promoter in a solution’ in claim

39, step b) lacks antecedent basis.” (Answer 16.) In addition, the Examiner also asserts that the phrase “‘the skeletal muscle cell of the limb distal to the applied pressure’ in step b) of claim 39, lacks antecedent basis.” (*Id.*)

There is no specific requirement for strict antecedent basis, only that the claims, when read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. We conclude step (b) of claim 39 would reasonably apprise the skilled artisan as to the meets and bounds of the claimed subject matter, and the rejection is reversed.

Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36, and 39-42 stand rejected under 35 U.S.C. § 112, first paragraph, because

the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a protein operably linked to a promoter and wherein said protein is expressed to detectable levels in muscle cells of said limb, does not reasonably provide enablement for applying any “non-invasive pressure” against the skin of the limb, injecting a viral vector into a blood vessel in the limb and expressing the viral vector in skeletal muscle cells as claimed or applying a cuff proximal to the site of injecting. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

(Answer 8-9.)

In setting forth the enablement rejection, the Examiner goes through the factors set forth by the Federal Circuit, our reviewing court, in *In re*

Wands, 858 F.2d 731 (Fed. Cir. 1988) (Answer 8-14). The facts that should be considered in determining whether a specification is enabling, or if it would require an undue amount of experimentation to practice the invention include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Wands*, 858 F.2d at 737.

The basis of the Examiner's rejection appears to be that the "claims are not enabled for their full breadth because they use open language and encompass applying a tourniquet to the skin while passing it under the inguinal ligament during a surgical procedure and using a perfusion pump to deliver adenovirus as taught by Milas² who taught such a method did not provide delivery to skeletal muscle as claimed." (Answer, 18-19.)

Specifically, according to the Examiner, "[b]ecause of the open language, step (a) also encompasses applying a tourniquet to the skin of the leg ('non-invasively') while applying the tourniquet invasively." (*Id.* at 10.) The Examiner argues that "[a]pplying a tourniquet as described by Milas also meets the limitation of step (a) because step (a) uses open language and does not exclude applying pressure against the skin while passing the tourniquet under the inguinal ligament; step (a) is not limited to applying pressure only against the skin." (*Id.* at 11.) Moreover, Milas also meets the limitation of "impeding blood flow into and out of the limb", the Examiner

² Milas et al., "Isolated Limb Perfusion in the Sarcoma-bearing Rat: A Novel Preclinical Gene Delivery System," *Clinical Cancer Research*, Vol. 3, pp. 2197-2203 (1997).

argues, “because step (a) uses open language and does not exclude partially impeding blood flow into and out of the leg using a tourniquet while using a perfusion pump and because the tourniquet blocks blood flow between the leg and the rest of the body; step (a) is not limited to impeding *all* blood flow into and out of the leg.” (*Id.*)

The Examiner concludes”

One of skill would recognize that steps (a) and (b) as claimed encompass the steps taught by Milas but would not result in expression as claimed. Given the breadth of steps (a) and (b) taken with the teachings of Milas and the lack of teachings in the specification regarding how to overcome the teachings of Milas and obtain expression in skeletal muscle cells using adenovirus, it would have required one of skill undue experimentation to determine how to perform the steps of (a) and (b) as broadly claimed using an adenovirus and obtain expression as claimed. While non-operative embodiments are allowed in a claim, steps that are not enabled in the specification as originally filed are not. The steps in the methods claimed do not exclude using a perfusion pump while applying a tourniquet. As such, the steps in the methods claimed encompass the steps of Milas and, therefore, encompass non-enabled steps. No amount of experimentation would allow one of skill to obtain expression of an adenovirus in skeletal muscle cells by applying a tourniquet while using a perfusion pump as encompassed by the claims.

(*Id.* at 13-14.)

In view of the interpretation of “non-invasive” as discussed above in the analysis of the rejections under 35 U.S.C. § 112, first paragraph, we conclude that the claims cannot be so broadly interpreted such that they read on the method of Milas.

In addition, claims 1 and 39 require that non-invasive external pressure be applied against the skin of a limb of the mammal such that blood

flow to and from the limb is impeded. As pointed out by Appellants, Milas uses a perfusion pump that is positioned below the plane of the animal to allow venous outflow (Br. 5, citing Milas, p. 2199, column 1). In fact, as also noted by Appellants, Milas notes that inserting a solution containing adenovirus into an artery while allowing brisk outflow through a vein is critical to their procedure (Br. 6, citing Milas, p. 2202, col. 1). Again, to interpret the claims as allowing the venous outflow obtained using the perfusion pump of Milas would read the limitation that non-invasive external pressure be applied against the skin of a limb of the mammal such that blood flow to and from the limb is impeded out of the claim, and we decline to do so.

Thus, the Examiner erred in interpreting the claim broadly enough to encompass the method of Milas, and then requiring Appellants' Specification to enable that Method. Thus, the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, is reversed.

Claim 39 stands rejected under 35 U.S.C. § 102(e) as being anticipated by Draijer-van der Kaaden.³

Draijer-van der Kaaden is cited for teaching the administration of a adenovirus encoding LacZ operably linked to a promoter into the femoral vein of a rat using a perfusion pump while applying a tourniquet around the groin (Answer 16). According to the Examiner, "Applying the tourniquet to the groin as taught by Draijer-van der Kaaden is equivalent to 'applying pressure non-invasively against the skin of a limb' as claimed because it did

³ Draijer-van der Kaaden, U.S. Patent No. 6,495,131 B1, issued December 17, 2002.

not injure the leg and because Draijer-van der Kaaden did not teach the tourniquet went under the blood vessel.” (*Id.* at 17.)

The burden is on the Examiner to set forth a prima facie case of unpatentability. *In re Glaug*, 283 F.3d 1335, 1338 (Fed. Cir. 2002). In order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

Claim 39 requires “applying pressure non-invasively against the skin of the limb thereby impeding blood flow into and out of the limb.” Draijer-van der Kaaden teaches applying pressure to the groin, and the Examiner does not explain how the groin reads on a limb. Thus, as Draijer-van der Kaaden does not teach applying pressure non-invasively against the skin of a limb thereby impeding blood flow into and out of the limb, it does not teach each limitation of claim 39, and we are compelled to reverse the rejection.

CONCLUSION

In summary, we find that the Examiner has not set forth a prima facie case of unpatentability, and the rejections on appeal are reversed.

REVERSED

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